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II. Peripheral and Central Neural Stimulation

M. VELASCO and D. B. LINDSLEY

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Effect of Thalamocortical Activation on Recruiting Responses * **

II. Peripheral and Central Neural Stimulation

M. VELASCO *** and D. B. LINDSLEY
(Los Angeles, California)

IN A PREVIOUS study Velasco *et al* [15] showed that a single locus of reticular stimulation produced a generalized blocking or attenuation effect on cortical recruiting and augmenting responses evoked by low-frequency thalamic stimulation regardless of where the responses were initiated in the thalamus or where they were recorded on the cortex. This blocking effect was specifically on the incrementing portion of the recruiting response and the waxing and waning characteristic of the recruiting train. It was concluded, therefore, that the interference by reticular activation on thalamocortical mechanisms was related to the incrementation process and periodic modulation of the recruiting responses.

The present investigation was concerned with the question of whether activation induced by central or sensory activation affects cortical recruitment in the same way as reticular formation activation.

Method

Experiments were performed on 20 cats, immobilized either by intravenous administration of gallamine triethiodide (Flaxedil) under local Procaine anesthesia or by a high cervical transection between C1 and C2 Cortical recruiting responses were evoked by stimulation of N. centralis medialis, N. centrum medianum, and N. centralis lateralis. These thalamic nuclei were stimulated through small-tip (100 to 125 μ) stainless steel, parallel electrodes. Stimuli consisted of 2 to 3 sec trains of 8/sec square pulses of 0.5 msec duration with intensity adjusted to evoke bilateral cortical responses. Responses were recorded monopolarly from stainless steel screws in the skull. The reference electrode was a clip attached to the stereotaxic frame.

The effect of visual, auditory, olfactory, proprioceptive, tactile, and nociceptive stimulation was recorded. Visual stimulation consisted of repetitive flashes of 50/sec. Flashes were administered by a

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Grass Model PS-1 photostimulator. Pupils were paralyzed and dilated with 10 % homatropine.

Auditory stimulation was a 0.5 to 2 sec duration 1.000 c/sec tone delivered through earphones attached to hollow ear bars of the stereotaxic instrument. An audio oscillator and an ultralinear audio-monitor system, Grass Model AM-3, was used as the sound generator. The intensity of the tone was approximately 80 db.

Olfactory stimulation consisted of a puff of air applied directly to the nasal cavity through a polyethylene catheter introduced into the nostril or into the frontal sinus. Proprioceptive activation was produced by stretching the jaw or during the spontaneous twitching which occurred upon release from Flaxedil, about 45 to 60 minutes after injection of 16-19 mg of the curarizing agent.

Central stimulation was delivered to the frontal cortex (anterior sigmoid and proreus gyri), cerebellar cortex (anterior lobe), basolateral amygdaloid complex, head of the caudate nucleus, N. centrum medianum. and the mesencephalic reticular formation. Cortical stimulation was delivered through silver ball electrodes placed on the pial surface of the frontal and cerebellar cortices. Subcortical stimulation was delivered through concentric bipolar electrodes insulated except at the tips. All central stimuli consisted of 150 c/sec square pulses of 0.5 msec duration with intensity adjusted to observe blocking of the recruiting responses. Individual pulse intensity was measured and maximal intensity of stimulation never exceeded 1.800 μA.

Electrical stimulation was administered by a Grass S4 stimulator through an SIU4 isolation unit. Cortical responses were recorded simultaneously on a Grass Model IIID eight-channel electroencephalograph and a Tektronix Model 502 dual beam oscilloscope, with Tektronix Model 122 preamplifiers.

At the conclusion of each experiment, electrode placements were marked by passing anodal current (2 mA for 15 sec). The brain was then perfused with saline followed by a 10 % solution of formalin. Thalamic and reticular formation placements were grossly delineated by frozen section and were assessed finally in Nissl preparations according to the atlas of Jasper and Ajmone-Marsan.[6]

Results

Recruiting responses were elicited by stimulation of three diffuse thalamic projection nuclei showing different amplitude distributions over cortical areas. N. centralis medialis (NCM) evoked maximal amplitude responses in both frontal areas (ant. sigmoid gyri), N. centrum medianum (CM) evoked maximal amplitude responses in the frontal region ipsilateral to the locus of stimulation, and N. centralis lateralis (CL) evoked maximal amplitude responses in the ipsilateral suprasylvian areas.

Experiments were planned to provide information on the following: (1) the effect of visual, auditory, olfactory, and proprioceptive stimulation on recruiting elicited by stimulation of a single thalamic nucleus; (2) the effect of neocortical, rhinencephalic, diencephalic, mesencephalic, and rhombencephalic electrical stimulation on recruiting responses elicited by stimulation of a single thalamic nucleus; (3) the comparative effect of sensory and central brain activation on recruiting elicited by stimulation of a single thalamic nucleus; (4) the comparative effect of sensory and central brain activation on recruiting elicited from two different thalamic nuclei.

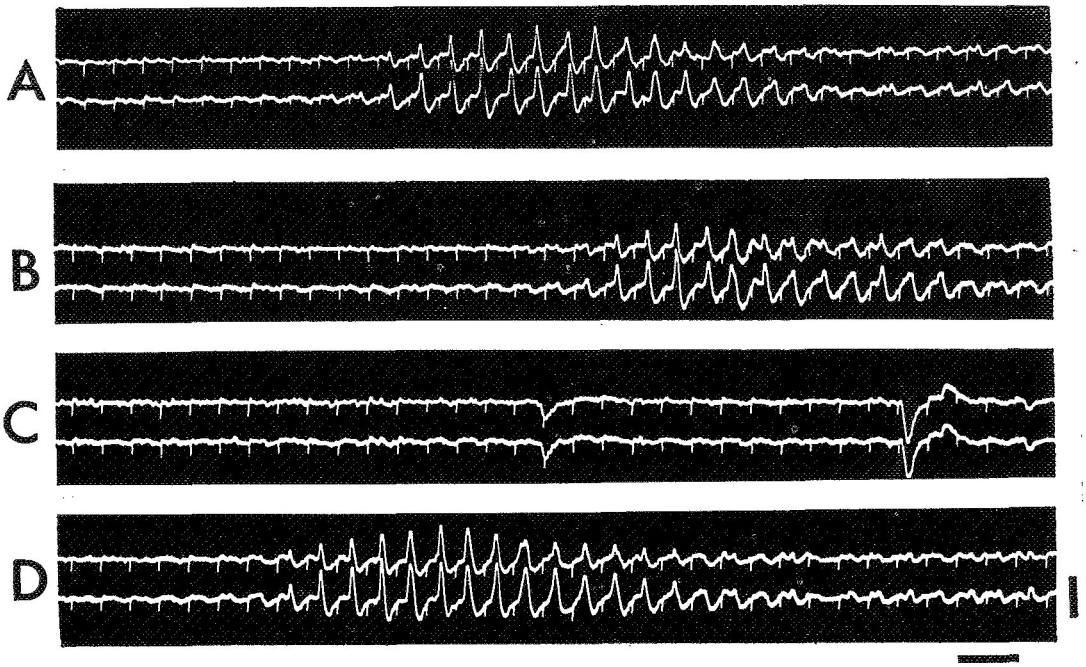


FIG. 1.—*Effect of Flaxedil and return of muscle action and proprioception on recruiting responses.* A, B, C, D: Cortical recruiting responses elicited by right N. centrum medianum stimulation and recorded at the left (upper trace) and right (lower trace) anterior sigmoid gyri. In A recruiting responses are shown immediately after intravenous injection of Flaxedil (18 mg.) B was 45 minutes later, C was 54 minutes later, and D was immediately after a second injection of Flaxedil (18 mg). At 45 minutes rate of development of recruiting was slower. At 54 minutes, with muscle action and proprioception returning, spontaneous jerks appeared in the course of the recruiting stimulation and recruiting responses were not obtained. With renewal of Flaxedil level for paralysis and loss of proprioception (D) recruiting returned. Calibrations, 200 μV and 1 sec.

The Effect of Sensory Activation

In these experiments, particular care was taken to maintain the animal in an environment deprived of as much sensory stimulation as possible. The preparations were procainized at surgical incisions and pressure points every two hours, maintained at normal temperature, and isolated from light and noise. Flaxedil administration was carefully controlled since it was found to be an important factor in the blocking of recruiting responses. Figure 1 shows the effect on recruiting responses of Flaxedil administration and the effect of its release and the subsequent return of muscle action and proprioception.

Shortly after Flexedil injection, responses appeared stable and were elicited at low threshold values (Fig. 1A); 45 to 60 minutes after a single injection (16 to 20 mg), recruiting responses incremented more slowly than they did immediately after injection (Fig. 1B). As the effects of the Flaxedil disappeared and muscle action and proprioceptive stimulation

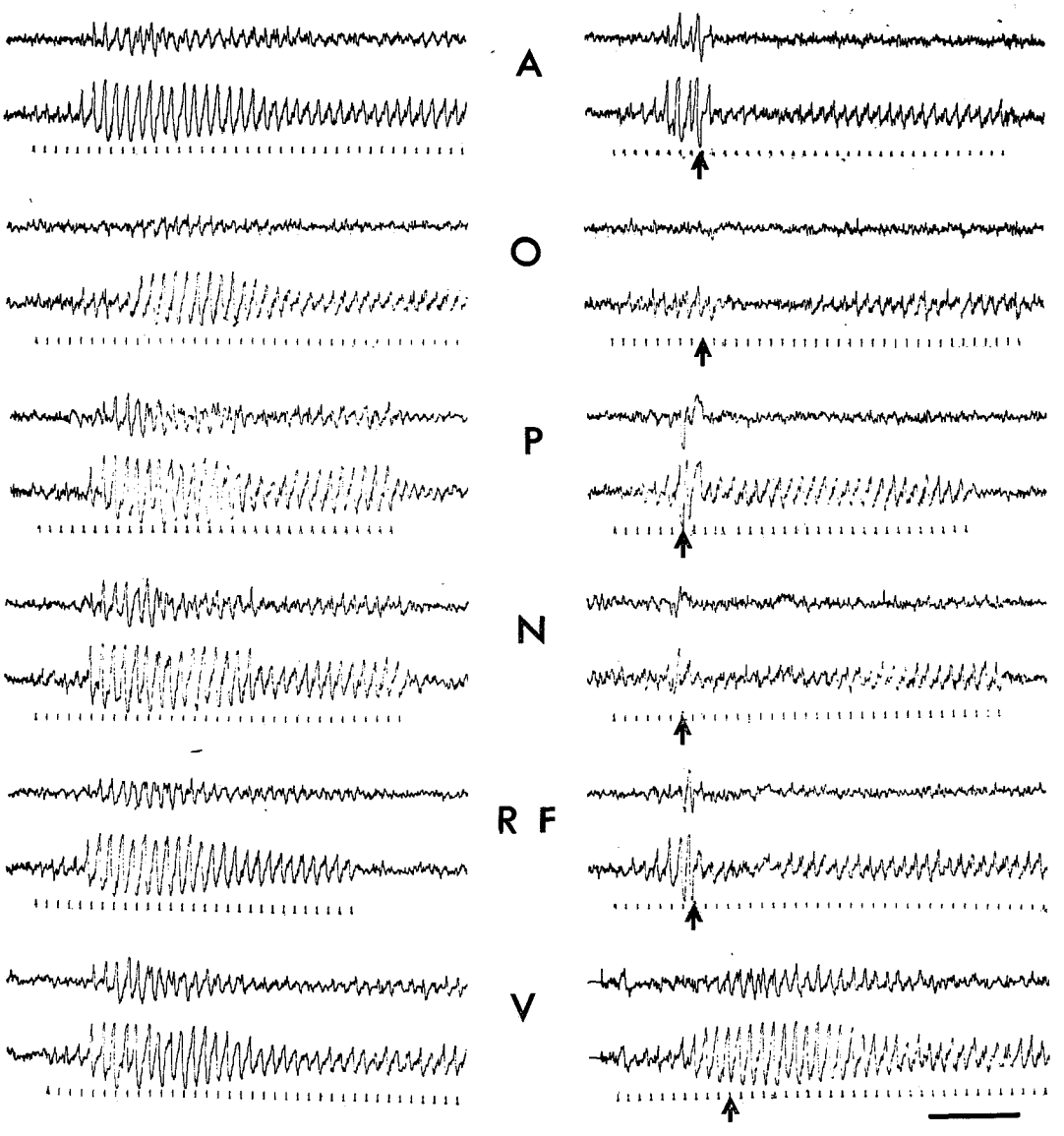


FIG. 2.— *Blocking of recruiting responses by sensory stimulation. Left,* cortical recruiting responses elicited by stimulation of right N. centrum medianum (8/sec) and recorded at posterior (upper trace) and anterior (lower trace) right sigmoid gyri. *Right,* effect of sensory stimulation on recruiting. Auditory (A), olfactory (O), proprioceptive (P), and nociceptive (N)stimulation all blocked thalamocortical recruiting. Reticular formation (RF) stimulation at 150/sec blocked recruiting similarly. Visual stimulation (V), in this case did not block recruiting responses. Arrows indicate onset of sensory and RF stimulation. All recordings were from the same animal. Calibrations, 200 μV and 1 sec.

returned, approximately 1 hr after initial Flaxedil, recruiting could not be elicited (Fig. 1C). The response returned to control values when Flaxedil was readministered (Fig. 1D). This finding is in agreement with the opinion of Hodes [5] who suggested that Flaxedil and other curarizing agents facilitate synchrony of the electrocortical activity not because of a direct action on central structures but because of a blocking of proprioceptive mechanisms which appear to be important in the maintenance of the wakeful state. This also implies that the blocking of recruiting observed in chronic preparations concomitant with motor orientation reactions may be due, in part, to the proprioceptive feedback from neck muscles.[3, 16]

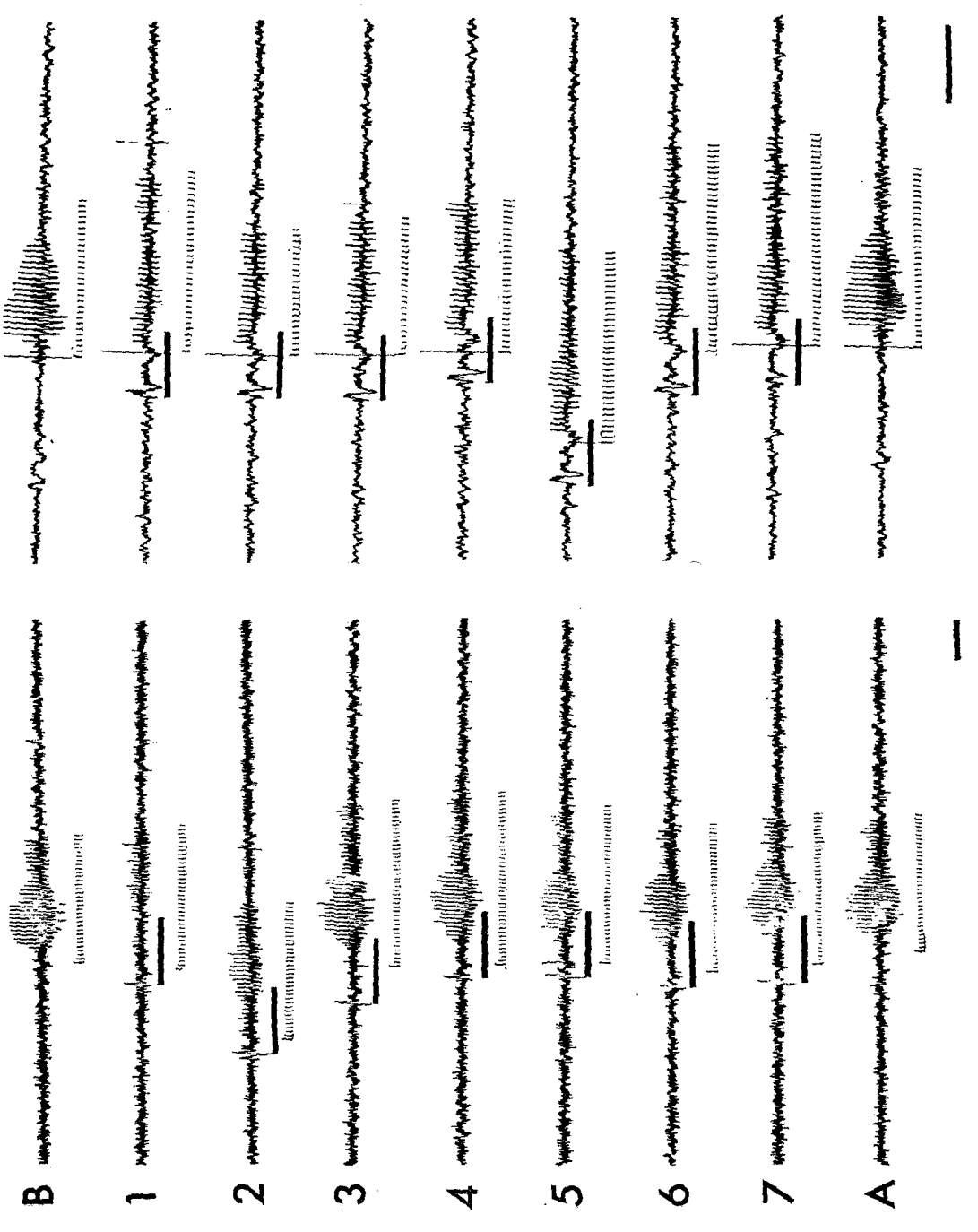
The effect of sensory activation on recruiting responses is shown in figure 2. Auditory (A), olfactory (O), proprioceptive (P), and nociceptive (N) stimulation under similar conditions blocked the recruiting responses. In all cases sensory stimulation blocked incremental and waxing and waning properties of the responses leaving only non-incremental portions. In some experiments, visual stimulation failed to block recruiting responses (Fig. 2V). No explanation can be given for this fact since in all cases a very bright light was presented with a wide range of frequencies (1 to 50 c/sec), the pupils were completely dilated, and evoked potentials at the lateral gyrus were driven by stimulation. In two of six experiments, however, blocking of recruiting did occur with photic stimulation.

It is evident that novel stimulation produced a clear-cut blocking of the recruiting responses, but subsequent, regularly repeated, stimulation in the same sensory modality failed to produce the same effect. Figure 3 (left) shows the effect of a 1.000 c/sec tone on recruiting. Initially, on trial 1, the tone blocked the responses, but subsequently (trials 2-5) it only delayed the onset and rate of incrementation and finally, on trials 6 and 7, there was little effect except for a slight delay in onset of recruiting. In contrast, reticular formation stimulation blocked recruiting whenever, and as many times as, it was presented (Fig. 3, right).

The Effect of Central Stimulation

Typical EEG desynchronization was produced by electrical stimulation of

FIG. 3.— *The effect of novel and repeated neural activation on recruiting responses. Left,* novel auditory stimulation (1) blocked recruiting responses but during repeated stimulus presentations (2-7) failed to block the responses. B to A, recruiting responses produced every 40 seconds by 8/sec stimulation of right N. centrum medianum and recorded at right anterior sigmoid gyrus. The typical recruiting responses before (B) and after (A) regularly repeated auditory stimulations are shown. Whereas in trial 1 auditory stimulation effectively blocked recruiting, in trials 2-7 the same auditory stimulation progressively was less effective in blocking recruiting and only delayed the onset of the recruiting process. *Right,* both novel (1) and repeated (2-7) stimulation of the reticular formation (150/sec) was sufficient to block the recruiting process and the effect remained constant throughout. Data were obtained from the same cat. Calibration, 2 sec.


B
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A

the following structures: frontal (motor) cortex, amygdala, caudate nucleus, N. centrum medianum, cerebellar cortex, and mesencephalic reticular formation. In the same way, high frequency stimulation of these structures blocked recruiting responses (Fig. 4). Under similar parameters of stimulation (150 c/sec; 0.5 msec pulse), however, the threshold intensity necessary to block recruiting varied from 60 to 1800 μA. For instance, stimulation of the periaqueductal portion of the reticular formation (RF) required an intensity of 80 μA to block recruiting, whereas frontal cortex (FC) stimulation required an intensity of 1800 μA. Other structures required intermediate intensity values, and there was a hierarchy of effectiveness in the blocking of the recruiting responses which seemed to be organized in the following order: mesencephalic, rhombencephalic, diencephalic, rhinencephalic and telencephalic.

The establishment of such a hierarchy is complicated, and the fact must be considered that the threshold to induce blocking of recruiting for a given structure depends in part upon the position of the electrodes within that structure and the characteristics of the stimulation itself. For example, the threshold on the anterior sigmoid gyrus was higher if the stimulating electrodes were on the surface rather than when one electrode was on the surface and the other penetrating the cortex or if the electrodes were more laterally placed. In addition, caudate stimulation seemed to be more effective at 50 c/sec than at 150 c/sec. Regardless of these facts, the results still indicate that the threshold for blocking of recruiting is different according to the locus of stimulation.

It was pointed out that the ability of a given sensory stimulus to block recruiting depends on whether it is novel or repeated (Fig. 3). Threshold reticular stimulation, however, had the same ability to block recruiting from the first to the twentieth or thirty-sixth stimulus. Usually, after 36 to 40 trials, however, the control values of recruiting were depressed, and the ability of a structure to block the responses could not be evaluated.

Effect of Sensory and Central Stimulation on a Given Recruiting Response

The effect of arousal on thalamocortical recruiting, in relation to the particular aspects of the process which are blocked, may be observed in figure 5. Recruiting responses were produced by right centrum medianum (CM) stimulation, and maximal amplitude responses were obtained on the right anterior sigmoid gyrus ipsilateral to the thalamic locus of stimulation (upper trace). This area was responsive to single shock, and the recruiting (type II) had a latency of 15 msec, an initial positive component, and a rapid development to maximal amplitude. Contralateral recruiting showed type I characteristics, that is, no response to single shock, monophasic and negative, longer latency, and slower development.

Stimulation of different structures, including frontal cortex, cerebellar

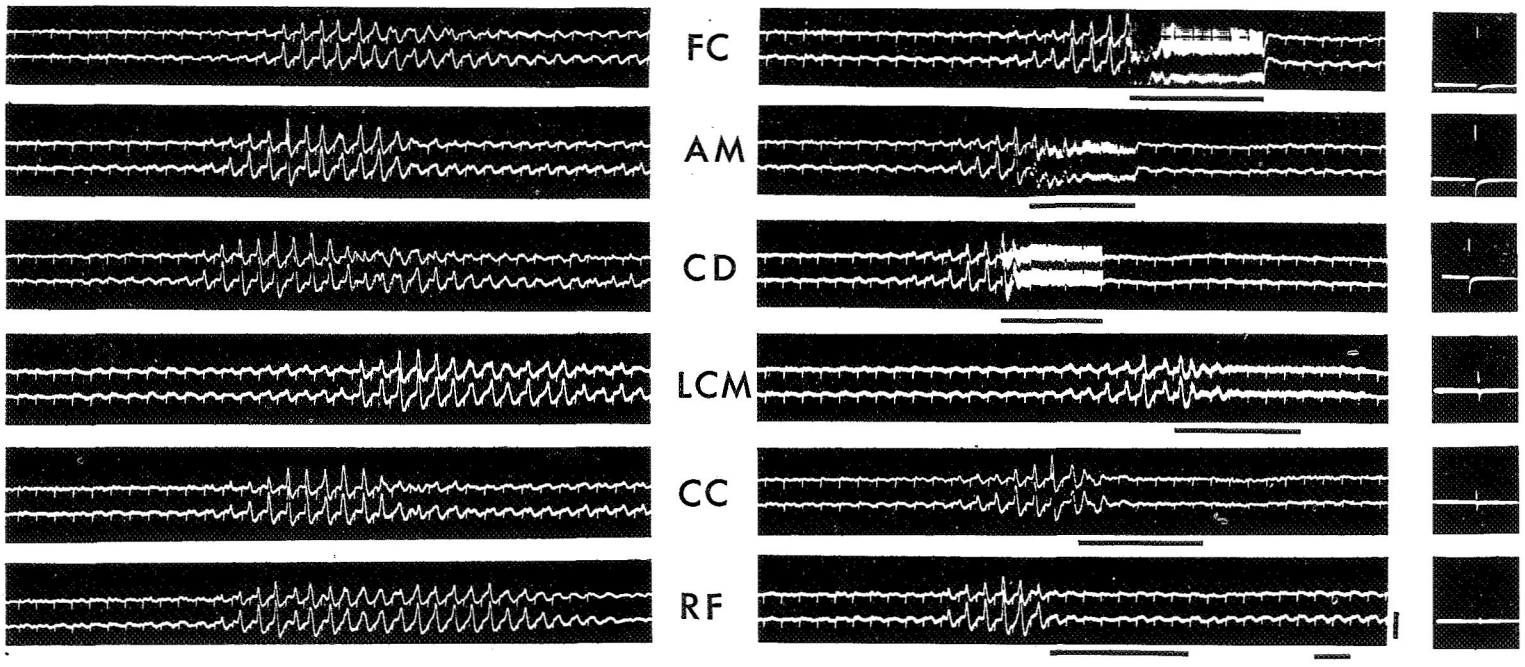

FIG. 4.— *Central (telencephalic, rhinencephalic, diencephalic, rhombencephalic and mesencephalic) activation blocked recruiting. Left,* cortical recruiting responses elicited by right N. centrum medianum stimulation (8/sec) and recorded at left (upper trace) and right (lower trace) anterior sigmoid gyri. *Right,* high frequency stimulation of different central structures blocked the recruiting process. FC, frontal cortex; AM, basolateral amygdala; CD, head of caudate nucleus; LCM, left N. centrum medianum; CC, cerebellar cortex; RF, brain stem reticular formation. All structures were stimulated with trains of 150/sec pulses of 0.5 msec duration and at threshold necessary to block recruiting. All recordings were from the same animal. Calibrations, time 1 sec; amplification 200 μV; stimulation intensity in μA at extreme right, RF, 80; CC, 360; LCM, 600; CD, 1.200; AM, 1.600; FC, 1.800.

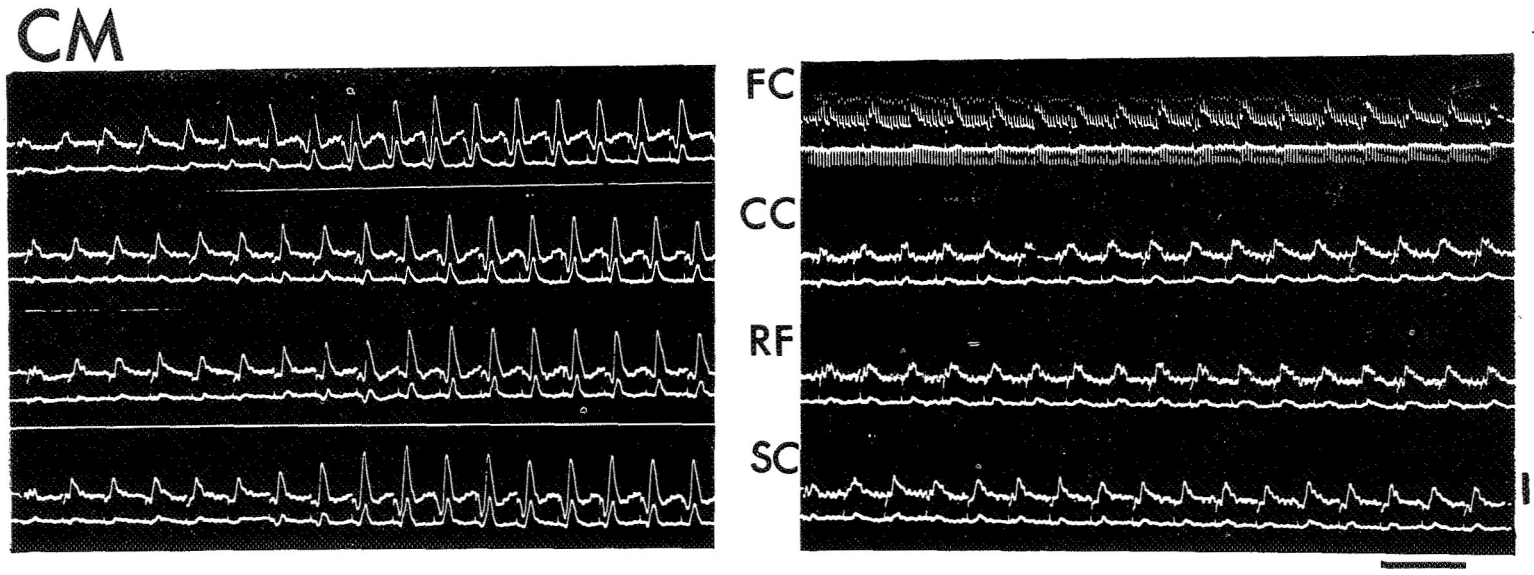

FIG. 5.— *Central and peripheral neural activation blocked the same aspects of the recruiting process. Left,* cortical recruiting responses elicited by 8/sec stimulation of right N. centrum medianum (CM) and recorded at right (upper trace) and left (lower trace) anterior sigmoid gyri. *Right,* effect upon recruiting of high frequency stimulation of different central structures. FC, frontal cortex; CC, cerebellar cortex; RF, mesencephalic reticular formation. SC, shows the effect of a single shock applied to the sciatic nerve 0.5 sec before this record. At the right anterior sigmoid gyrus recruiting responses have an initial positive component and maximal amplitude was attained after 8 to 11 pulses (type II). In contrast, recruiting responses at the left anterior sigmoid gyrus are monophasic and negative and attain maximal amplitude slowly (type I). Central and peripheral neural activation blocked incrementation in both type I and type II recruiting. In type I recruiting, the responses were abolished, and in type II recruiting the responses were reduced to non-incremental components. All recordings from the same animal. Calibrations, 200 μV and 1 sec.

cortex, reticular formation, and sciatic nerve, blocked recruiting in the same way. That is, in all cases, the incremental and waxing and waning features of the responses disappeared, contralateral responses were abolished, and ipsilateral responses were reduced to non-incremental potentials. These effects were the same as those obtained from stimulation of a single point in the reticular formation.[15] Arousal or activation, therefore, seemed to affect thalamocortical systems qualitatively as a unit, regardless of the way in which it was induced.

It is of interest to note that arousal evaluated by the blocking of recruiting responses was the same as that induced by reticular or amygdaloid stimulation (Fig. 4). The effect of amygdaloid stimulation was produced using more than required for reticular stimulation but with an intensity low enough not to induce epileptic afterdischarge. Presumably the effect on the ipsilateral frontó-temporal cortex observed by Feindel and Gloor,[4] when stimulating the amygdala, is a different phenomenon, unrelated to the ability of the amygdala to induce general electrocortical arousal.

The Effect of Sensory and Central Activation on Different Recruiting Responses

In order to test the effect of arousal on recruiting recorded at different cortical sites and initiated at different thalamic loci, the effect of arousal on recruiting originating from N. centrum medianum (CM) and N. centralis lateralis (NCL) was studied. Maximal amplitude recruiting responses appeared in both frontal areas upon CM stimulation. In contrast, maximal amplitude responses appeared in the ipsilateral area upon NCL stimulation. Blocking of recruiting was produced by stimulation of the caudate nucleus, the amygdala, centrum medianum, and the reticular formation. It is noteworthy that blocking of recruiting occurred with stimulation of all of these structures and also that the pattern of blocking varied according to the characteristics of the recruiting responses. For a given recruiting response (CM or NCL), however, the pattern of blocking was the same regardless of the way in which it was induced.

Discussion

Moruzzi and Magoun,[9] and subsequently Jasper *et al*[7] and Velasco *et al*,[15] observed that blocking of recruiting may be induced at different arousal sources and may be considered equivalent to the blocking of spontaneous spindles, thus being an index of electrocortical arousal. The present paper extends the observations of blocking of recruiting by considering other structures which are known to produce EEG desynchronization, that is, the frontal cortex,[1, 2] the amygdala,[4, 8] the caudate nucleus,[10] and the cerebellar cortex.[9]

Electrocortical arousal evaluated by blocking of recruiting responses is quantitatively different depending upon whether it is induced centrally or peripherally, whether the stimulation is novel or repetitive, and whether the intensity of stimulation is low or high.

On the other hand, the arousal reaction is qualitatively the same regardless of the way in which it is induced. In this respect, arousal is generalized to all thalamic and cortical areas but is only effective in blocking the waxing and waning features of the recruiting responses.

The facts suggest that electrocortical arousal is a unitary response. That is, it may be elicited by different sources of peripheral and central activation, and when such activation reaches a certain level, it triggers a common mechanism which produces a stereotyped cortical reaction, no longer dependent upon the way in which the mechanism was activated. According to Moruzzi and Magoun,[9] this mechanism depends on the brain stem reticular formation in which descending and ascending influences in the brain are integrated. The fact that arousal is generalized and is able to block recruiting responses differentially initiated in the thalamus and differentially distributed on the cortex suggests that blocking of recruiting is not a competitive interaction of responses at the cortex itself but is more likely an interaction at some common locus. This mechanism may correspond to the thalamo-orbitocortical system believed to be involved in the process of incrementation and periodic modulation of cortical responses.[11-14]

Summary

In twenty unanesthetized, immobilized cats, blocking of thalamocortical recruiting responses was studied according to the way in which the phenomenon was induced.

Like EEG desynchronization, blocking of recruiting occurred when arousal was induced centrally or peripherally. Auditory, visual, proprioceptive, and nociceptive activation or high frequency stimulation of telencephalic, rhinencephalic, diencephalic, rhombencephalic, and mesencephalic structures all blocked recruiting responses.

Blocking of recruiting was quantitatively different depending on whether it was centrally or peripherally induced, the threshold or intensity required to induce it, and whether the stimulation was novel or repetitive.

Blocking of recruiting was qualitatively similar, being generalized and affecting only the waxing and waning characteristics of the phenomenon. Thalamocortical arousal seems to be a unitary function induced by different means but following a general pattern, possibly mediated by a common reticulo-thalamo-orbitocortical system.

Resumen

En 20 gatos no anestesiados e inmovilizados se estudió el bloqueo de la respuesta de reclutamiento talamocortical en relación a los diferentes modos de producir este fenómeno.

La respuesta de reclutamiento se bloqueó, junto con la desincronización cortical, cuando se provocó despertar (o *arousal*) central o periféricamente. La respuesta de reclutamiento pudo ser bloqueada por activación auditiva visual propioceptiva o nociceptiva como también por estimulación a alta frecuencia de estructuras telencefálicas, rinencefálicas, diencefálicas, romboencefálicas o mesencefálicas.

El bloqueo de la respuesta de reclutamiento tenía variaciones cuantitativas que dependían de si era inducido central o periféricamente, el umbral e intensidad necesaria para inducir y si la estimulación era nueva o repetida.

Cualitativamente, el bloqueo de reclutamiento era similar, siendo generalizado y afectando sólo la característica de crecimiento y disminución alternada de la amplitud. El despertar talamocortical parece ser una función unitaria inducida por distintos medios, pero que sigue un esquema (modalidad) general posiblemente mediado por un sistema común retículo-tálamo-órbito-cortical.

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